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COMPRESSED MEDICAL GASES GUIDELINE

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Room 9B-03
5600 Fishers Lane
Rockville, MD 20857

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COMPRESSED MEDICAL GASES GUIDELINE

PURPOSE

This guideline describes practices and procedures for compressed medical gas (CMG) fillers that constitute acceptable means of complying with certain sections of the current good manufacturing practice (CGMP) regulations for drug products (21 CFR Parts 210 and 211).

INTRODUCTION

This guideline, issued under 21 CFR 10.90, states principles and practices of general applicability that are not legal requirements but are acceptable to the Food and Drug Administration (FDA). A person may rely upon it with assurance of its acceptability to the FDA or may follow different procedures. Any person who chooses different procedures may, but is not required to, discuss the matter in advance with the FDA to preclude expending money and effort on activity that the FDA may later determine is unacceptable.

In the Federal Register of August 18, 1981 FDA published a notice of availability of the original guideline (June 1981). The guideline has been revised in response to comments submitted by the Compressed Gas Association. No other comments were received. FDA may further revise this guideline from time to time as the agency recognizes a need to do so through its regulatory efforts and through comments submitted by interested persons. If this guideline is further revised, FDA will publish a notice of availability of such revised guideline in the Federal Register.

READEX MICROFICHE

The format of this guideline remains the same. It follows specific requirements of 21 CFR Parts 210 and 211 with a discussion of practices and procedures which the FDA considers acceptable as a means of meeting the requirements. The guidance in this document is limited to those key sections of Parts 210 and 211 where there have been questions concerning acceptable ways for fillers of compressed gases to comply with the requirements therein. All sections of Part 211 are applicable to CMG fillers unless specifically exempted from the regulations.

EQUIPMENT DESIGN, SIZE, AND LOCATION

Requirement

Section 211.63 requires that equipment used in the manufacture, processing, packing, or holding of a drug product be of appropriate design and suitably located to facilitate operations for its intended use.

Guidance

One aspect of this requirement as related to the compressed medical gas (CMG) industry is that the equipment must be designed to assure that the proper gas is put into the correct container. FDA considers acceptable elements of design in this regard to include the following:

1. The CMG manifolds used are dedicated to a single gas (e.g. oxygen). For mixtures of two or more gases, the mixture is produced by filling the cylinders on manifolds dedicated to mixtures (e.g. nitrogen/oxygen).

2. The manifolds are equipped with fill connections that correspond only to the container valve connection for that particular gas or mixture of gases so that the wrong containers cannot be attached to the manifold. Other than for laboratory functions, adapters should be used only when filling containers on manifolds dedicated to the filling of mixtures. The use of manifold and container valve connections recommended in the Compressed Gas Association (CGA) pamphlet V-1 (ANSI B57.1; CSA-B96) "Compressed Gas Cylinder Valve Outlet and Inlet Connections" is an acceptable system for this purpose.

3. Filling of industrial and medical CMG containers (concurrently) on the same line is acceptable, provided the gas used for industrial purposes is equal to or higher in quality than the medical gas, and provided that containers have been prepared in accordance with the "Testing and Approval or Rejection of Drug Product Containers and Closures" and the "Drug Product Containers" sections of this guideline.

TESTING AND APPROVAL OR REJECTION OF COMPONENTS

Requirements

Section 211.84(a) requires that each lot of components be withheld from use until the lot has been sampled, tested, or examined as appropriate and released for use.

Section 211.84(b) requires that representative samples of each shipment of each lot be collected for testing or examination.

Section 211.84(d)(1) requires that at least one test be conducted to verify the identity of each component.

Section 211.84(d)(2) requires that each component be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of doing the testing itself, the manufacturer may accept a report of analysis from the supplier of a component, provided that the manufacturer conducts at least one specific identity test on the component, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

Guidance

Questions have arisen on how the above types of testing requirements are to be met in situations involving bulk deliveries of components which upon receipt are then commingled in bulk storage tanks with other lots of the same component. For instance, it may not be practical to sample a bulk liquefied gas either directly from a tank truck or directly from the bulk storage tank.

As an alternative to actually sampling and performing all required testing on each shipment of the component gas (i.e. either testing for all appropriate specifications, or receiving a report of analysis covering all such specifications and conducting an identity test) before it is released and added to bulk storage tanks, the following may be used to achieve compliance with these requirements.

1. In the case of a component which will be put in the final container as a single gas, the sample is taken either directly from the commingled lots in the bulk storage tank or indirectly by sampling from the first container filled from the commingled lots in the bulk storage tank after a new shipment has been added to the bulk tank. In the latter instance, testing the first container filled serves as both a component test and a finished product test (as long as all appropriate tests are performed).

2. In the case of separate components that will be used to produce a mixture of two or more gases, each component is tested before the mixture is put into containers. Samples are taken separately from the bulk storage tanks or from cylinders containing a single component.

TESTING AND APPROVAL OR REJECTION OF DRUG PRODUCTS

CONTAINERS AND CLOSURES

Requirements

Section 211.160(b) requires that laboratory controls include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug product containers and closures conform to appropriate standards of identity, strength, quality, and purity.

Section 211.84(d)(3) requires that containers and closures be tested for conformance with all appropriate written procedures.

Guidance

Drug product containers and closures for CMG's are typically reused numerous times. This presents some special considerations regarding appropriate specifications and testing for containers that customers return for refilling. Specifications and testing procedures for CMG drug product container/closure systems should include the following every time the container/closure system is refilled:

1. An odor test of each CMG cylinder before refilling to detect foreign odors (exceptions to this area are for anesthetic gases and carbon dioxide).

2. Visual external inspection of each valve and container for dents, arc burns, other damage, and oil or grease.

3. For each CMG cylinder manufactured to 3A or 3AA specifications, a dead ring test to determine if the gas cylinder walls have been weakened by interior rust. (Dead ring tests cannot be performed on cryogenic vessels nor on clustered cylinders, e.g. cradles which require special periodic hydrostatic testing).

4. For each CMG cylinder, a check to determine that the hydrostatic test is conducted at the interval required by the Department of Transportation (DOT) regulations (49 CFR 173.34). The testing intervals vary for different types of containers and gases. The DOT regulations require that each cylinder be marked with the date of the last hydrostatic test.

5. A check to determine that each container is of the proper color to correspond to any color-coding system employed such as that recommended by the CGA in their pamphlet C-9 Standard Color Marking of Compressed Gas Cylinders Intended for Medical Use in the United States.

6. A check of each cylinder or cryogenic vessel valve connection to determine that it is the proper type for the particular type of CMG involved.

DRUG PRODUCT CONTAINERS

Requirements

Section 211.94(c) requires that drug product containers be clean.

Section 211.94(d) requires that standards or specifications, methods of testing, and where indicated, methods of cleaning be written and followed for drug product containers.

Guidance

One factor to consider in regard to the above requirements is the possible presence of foreign gas residues in CMG cylinders before filling. An acceptable method of assuring that cylinders do not contain foreign gas residues is to pull a vacuum on each cylinder equal to 25 or more inches of mercury prior to filling with the CMG. (Cryogenic vessels are seldom completely emptied and need not be evacuated before filling.)

LABELING ISSUANCE AND PACKAGING AND LABELING OPERATIONS

Requirements

Section 211.125(c) requires that procedures be used to reconcile the quantities of labeling issued, used, and returned.

Section 211.130 requires that there be written procedures designed and followed to assure that correct labels, labeling, and packaging materials are used for drug products.

Guidance

CMG containers are not always completely relabeled when they are refilled. A previous container label, for instance, may be left on when the container is refilled, and the label need not be replaced unless it is outdated, damaged, or illegible. This practice has resulted in some questions concerning appropriate labeling controls and reconciliation procedures in such circumstances.

FDA considers it acceptable to continue to use existing labeling on CMG containers which are refilled if the procedures and controls provide for examining each container to assure that the labeling is in complete conformance to the currently approved master labeling and is otherwise suitable for continued use (e.g. it is undamaged, legible, and does not bear previous lot numbers).

Acceptable procedures for reconciling labeling in such circumstances would include recording the number of containers not relabeled but found acceptable on the basis of examining the previous labeling, as well as recording the number of containers actually relabeled. The quantities of labeling actually used for relabeling would be used to reconcile the quantities issued.

TESTING AND RELEASE FOR DISTRIBUTION

Requirements

Section 211.165(a) requires that for each batch of drug product, there be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, before release.

Section 211.165(c) requires that any sampling and testing plans shall be described in written procedures that include the method of sampling and the number of units per batch to be tested, and that the written procedure be followed.

Guidance

The following are acceptable types of plans for sampling and testing CMG's before release in certain types of filling operations. If nitrogen is a component of any mixture, a test for identity of the nitrogen is not required. Identity is assured by the filling procedure which introduces the nitrogen. If the filling procedure on the manifold makes possible an alternate gas, an identity test to establish the absence of that gas is to be performed.

1. In the case of a single CMG put into cylinders on a multi-cylinder manifold, at least one cylinder of product from each manifold filling is tested for identity and strength each time the cylinders are changed on the manifold.

2. In the case of a single CMG put into cylinders one at a time by individual filling operations, at least one cylinder of product for each uninterrupted filling operation cycle is tested for identity and strength. Examples of an uninterrupted filing operation cycle are one day's or one shift's production using the same personnel, equipment, and lot or commingled lots of component.

3. In the case of a finished CMG produced by combining two different gases in a cylinder, every cylinder is tested for the identity and strength of one of the gases, and at least one cylinder from each manifold filling is tested for identity of the other gas in the mixture.

4. In the case of a finished CMG produced by combining three different gases in a cylinder, every cylinder is tested for the identity and strength of two of the gases and at least one cylinder from each manifold filling is tested for the identity of the third gas in the mixture.

5. In the case of liquefied gas put into cryogenic vessels for delivery to users, each vessel is tested for identity and strength.

6. Liquefied gas cryogenic vessels which are retained by customers and serviced in place by refilling from mobile delivery tanks on a periodic basis need not be directly tested after filling if the filling firm has available suitable records of analysis covering the testing performed on a sample taken from their mobile delivery tank for identity and strength.

7. Each filled CMG cylinder is tested for leaks using an appropriate method, such as a leak detection solution applied to the valve area.

COMPONENT RECORDS

Requirement

Section 211.184(c) requires that records include an individual inventory record of each component, a reconciliation of the use of each lot of the component, and sufficient information to allow determination of which batches or lots of drug product are associated with each component.

Guidance

The agency recognizes that accurate component inventory records, including reconciliation of the use of each lot, are difficult to maintain for bulk liquefied gases. Complications include normal loss of the gas through vaporization, which may amount to 10 percent or more, and the commingling of component lots in bulk storage tanks.

FDA does not expect in such circumstances that the reconciliation will allow 100 percent accountability. The procedures for reconciling the use of components can allow for normal storage and operating losses as long as they require further investigation in the event of unexplained discrepancies such as losses beyond established normal levels.

BATCH PRODUCTION AND CONTROL RECORDS

Requirement

Section 211.188 requires that batch production and control records be prepared for each batch of drug product produced and include complete information relating to the production and control of each batch. These records include:

(a) An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed;

(b) Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including all particular information specified in this section.

Guidance

Questions have arisen on whether batch production and control records, which in the CMG industry are frequently in the form of a pumper's or filler's log, must contain a complete copy of all corresponding master production and control information.

It is acceptable for the batch production and control records to incorporate detailed production and control information by reference as long as significant processing steps are included in the batch records. As one example, it is suitable for the batch production and control record to provide an instruction such as "Evacuate cylinders per Standard Operating Procedure XYZ," if the details of Standard Operating Procedure XYZ appear in the master production and control records.

The requirement for supervising review of the batch production control records may be satisfied if the person in charge makes a daily review of these records and this review is noted on the records.

LABORATORY RECORDS

Requirement

Section 211.194(a)(2) requires that laboratory records include a statement of each method used to test the sample, indicating the location of data that establish that the methods meet proper standards of accuracy and reliability for the product tested. If the method employed is in a recognized standard reference such as the United States Pharmacopeia/National Formulary and is not modified, a statement of the method and reference will suffice.

Guidance

Several CMG's, being recognized in the United States Pharmacopeia/National Formulary, must meet the requirements contained in the official compendium. This does not mean, however, that the official tests must necessarily be used in testing for batch release purpose. Alternative methods may be employed to demonstrate satisfactory conformance to the appropriate requirements, but if a non-official test method is used for an official article, the laboratory records must document the fact that the method used is equal to or superior to the compendial method in terms of accuracy and reliability.

GLOSSARY

For purposes of this guideline, the following terms are given the stated meaning:

1. Container - A metal container designed to contain either liquefied or vaporized CMG.

2. Cryogenic vessel - A metal container designed to contain liquefied CMG at extremely low temperatures.

3. Compressed medical gas (CMG) - Any liquefied or vaporized gas alone or in combination with other gases which is a drug as defined by Section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (21 USC 321(g)(1)).

4. Cylinder - A metal container designed to contain CMG at a high pressure.

5. Dead ring test - Also called the "hammer test." A test used to determine the soundness of a cylinder by striking the side of the cylinder. If a clear bell like sound results, the cylinder is considered satisfactory. If a dull sound results the cylinder is not considered suitable for filling with a high pressure CMG.

6. Manifold - Equipment or apparatus designed to fill one or more CMG containers at a time.

7. Odor test - A test performed by opening a CMG cylinder valve to allow the CMG to flow into a cupped hand. The gas is then organoleptically examined by smelling for foreign gases. This test is not done on cylinders containing anesthestic gases or carbon dioxide.